

# A role for transcription factor NF- $\kappa$ B in autoimmunity: possible interactions of genes, sex, and the immune response

Elizabeth Dale,<sup>1</sup> Miriam Davis,<sup>2</sup> and Denise L. Faustman<sup>1</sup>

<sup>1</sup>Harvard Medical School and Massachusetts General Hospital-East, Boston, Massachusetts; and <sup>2</sup>School of Public Health and Health Services, George Washington University, Washington, District of Columbia

Submitted 12 July 2006; accepted in final form 2 September 2006

**Dale, Elizabeth, Miriam Davis, and Denise L. Faustman.** A role for transcription factor NF- $\kappa$ B in autoimmunity: possible interactions of genes, sex, and the immune response. *Adv Physiol Educ* 30: 152–158, 2006; doi:10.1152/advan.00065.2006.—Sex hormones have long been implicated in autoimmune diseases because women account for 80% of cases. The mechanism of hormonal action in autoimmunity is unknown. Drawing on genetic studies of autoimmune disease, this article discusses how both genes and sex hormones may exert their effects through the same general mechanism, dysregulation of transcription factor NF- $\kappa$ B, an immunoregulatory protein. Gene and hormone alterations of the NF- $\kappa$ B signaling cascade provide a unifying hypothesis to explain the wide-ranging human and murine autoimmune disease phenotypes regulated by NF- $\kappa$ B, including cytokine balance, antigen presentation, lymphoid development, and lymphoid repertoire selection by apoptosis.

nuclear factor- $\kappa$ B; autoimmune; apoptosis

THERE ARE SEX DIFFERENCES in the immune response and even more striking differences in autoimmune disease prevalence (Fig. 1). This sex difference is observed throughout the civilized world. Females have higher antibody levels than males, and they mount more robust immune responses to antigens. Females also have more CD4<sup>+</sup> lymphocytes and different cytokine profiles. Autoimmune diseases predominate among females, who account for nearly 80% of the 8.5 million Americans with autoimmune diseases (8, 73). Relatedly, hormonal shifts in pregnancy, menopause, and aging are associated with fluctuations in the course of autoimmune disease. Multiple sclerosis and rheumatoid arthritis, for example, improve during pregnancy, whereas lupus appears to worsen.

These observations have long implicated sex hormones in autoimmune disease etiology, course, or severity. Steroid receptors are found in immune cells and thus could provide a plausible pathway by which steroid hormones affect autoimmunity (53). However, the precise pathophysiological mechanisms by which sex hormones may exert their effects on autoimmune disease are largely unknown.

Enter the ubiquitous transcription factor NF- $\kappa$ B, which, since its discovery in 1986, has attracted wide interest as an immunoregulatory protein. NF- $\kappa$ B appears to be a central player in several autoimmune diseases, according to recent studies of genetic defects in autoreactive lymphoid cells (the immune cell types responsible for autoimmunity) in both

murine models of autoimmunity and humans with diverse forms of autoimmunity. Although the genes altering NF- $\kappa$ B appear to vary in different autoimmune diseases, usually decreased NF- $\kappa$ B activity in response to select cell surface cytokines is commonly observed (Fig. 2). A separate line of evidence has found that hormones also can influence NF- $\kappa$ B activity. This article discusses these two lines of evidence to hypothesize how both genes and steroid hormones might contribute to the pathogenesis of several autoimmune diseases through a common mechanism: reductions in NF- $\kappa$ B activity. Such decreases, in turn, can disrupt a range of disease-related immune functions, including cytokine balance, antigen presentation, lymphoid development, and apoptosis (6, 7).

As a background, NF- $\kappa$ B is found in the cytoplasm of immune cells in association with accessory proteins. Its mode of activation varies according to the immune cell type, its state of activation, or its developmental stage (54, 78). In peripheral T lymphocytes (T cells), NF- $\kappa$ B normally is blocked from entering the nucleus because its subunits are tightly bound to the inhibitory protein I $\kappa$ B- $\alpha$ . Upon the cellular induction by cytokines such as TNF and other signals, I $\kappa$ B- $\alpha$  undergoes a series of biochemical changes, including phosphorylation, ubiquitination, and then degradation by a proteasome. Once freed from I $\kappa$ B- $\alpha$ , activated NF- $\kappa$ B is able to translocate to the nucleus, where it binds within minutes to DNA, initiating the expression of various target genes, including those encoding cytokines (e.g., IL-2, TNF- $\alpha$ , and IFN- $\beta$ ), proapoptotic genes, or antiapoptotic genes (Fig. 2). The activation of life or death is essential for limiting T cell proliferation after antigen exposures and marking T cell balance in adulthood (Fig. 3). Sex and other steroid hormones and genes theoretically can influence NF- $\kappa$ B at any point in its activation, depending on the extracellular signal, receptor type, signaling pathway, and, ultimately, target genes. NF- $\kappa$ B activity also is determined by the immune cell type. Most monocytes and B cells, for example, constitutively express the active form of NF- $\kappa$ B, so its activation may be less dependent on proteasome function (44). T cells, in contrast, require NF- $\kappa$ B to be induced into an active form by the proteasome-dependent process noted above (59).

## Hormone Effects on NF- $\kappa$ B

Estrogen and progesterone have been shown, in various ways, to modulate NF- $\kappa$ B activity. Glucocorticoids, which are regulated in part by sex hormones, are immunosuppressants that also may modulate NF- $\kappa$ B activity (26). Both glucocorticoid and progesterone receptors block activation

Address for reprint requests and other correspondence: D. L. Faustman, Harvard Medical School and Massachusetts General Hospital-East, Bldg. 149, 13th St., Rm. 3602, Boston, MA 02192 (e-mail: faustman@helix.mgh.harvard.edu).

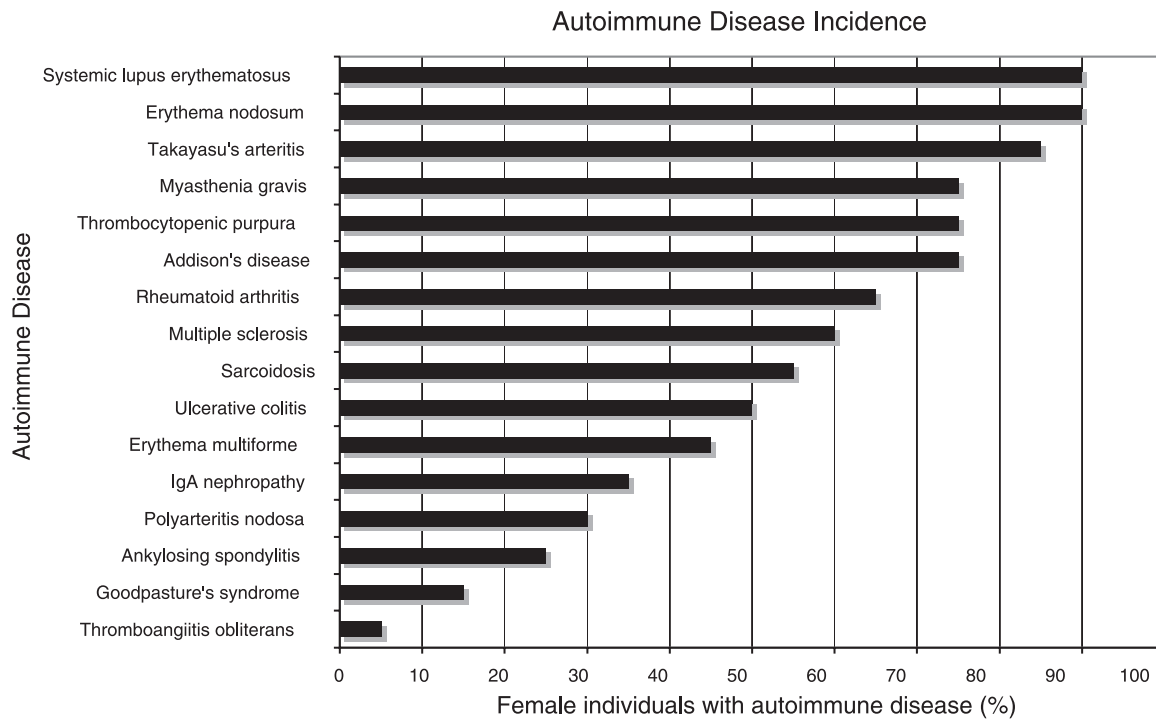


Fig. 1. Sex distribution of autoimmune diseases. For most, but not all, autoimmune diseases, females express the disease more frequently.

of NF-κB (12, 36, 58). Glucocorticoids also block NF-κB activation by another mechanism: transcriptional activation of IκB-α (5, 58). Transcriptional activation increases the synthesis of IκB-α, which quickly reunites with free NF-κB, thereby lowering levels of the latter. In contrast, levels of NF-κB and secreted TNF-α are dose dependently altered by 17β-estradiol. An increase in 17β-estradiol was sufficient to

have a possible physiological effect in the ratios of disease-causing cells with an altered cytokine balance (77). Auto-reactive cell populations are sometimes quantified by the ratios of T cell populations with secretion of proinflammatory versus anti-inflammatory cytokines. In an additional study (64), 17β-estradiol treatment of isolated cytotoxic human T cells showed a dose-dependent reduction of TNF-α

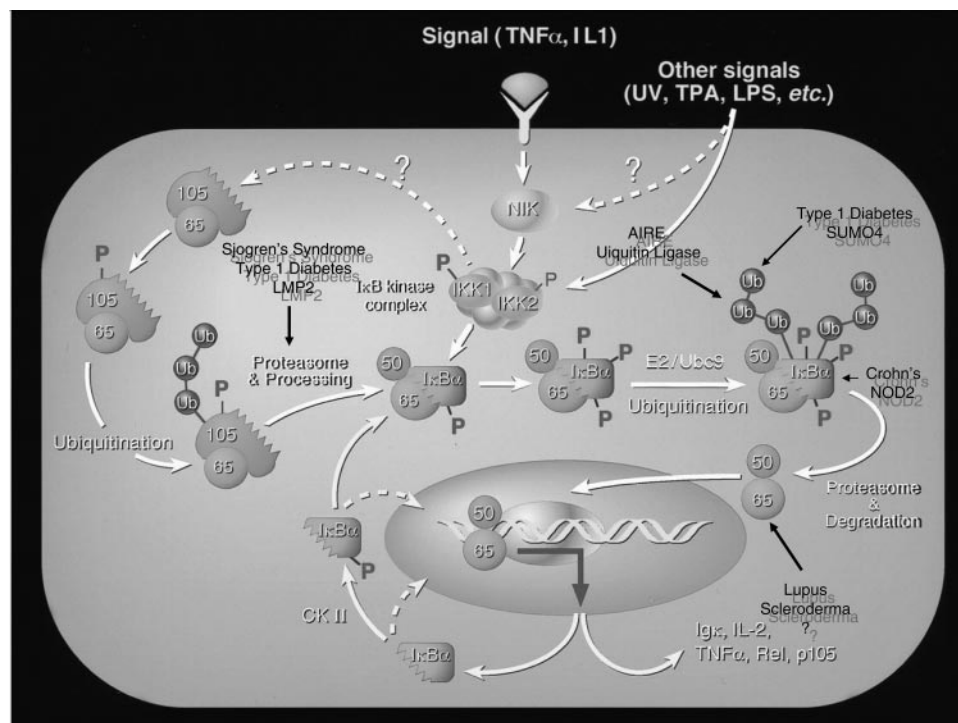
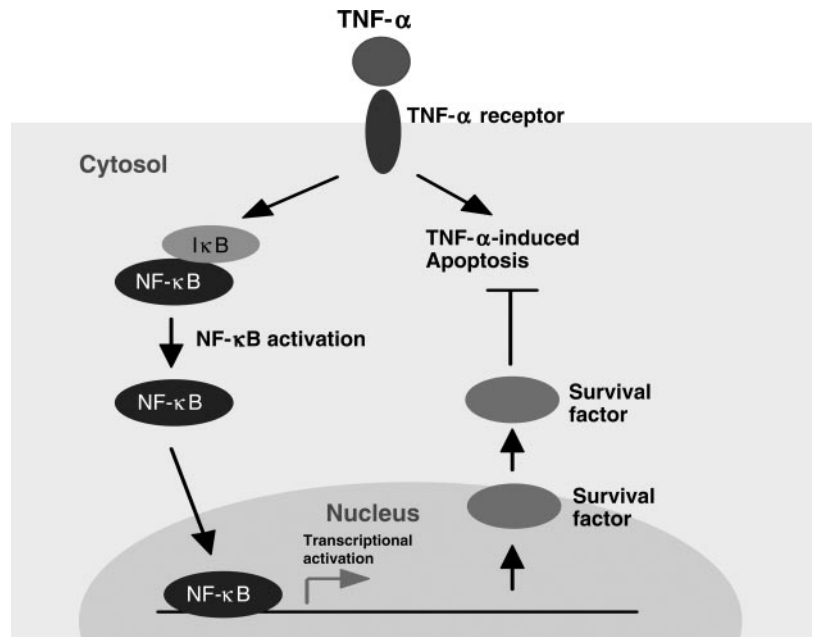


Fig. 2. Normal and altered cellular signaling of NF-κB in autoimmunity. In a normal immune cell in the periphery, exposure to TNF triggers a complex pathway of NF-κB activation that culminates in an active NF-κB dimer entering the nucleus, i.e., the p50/p65 complex. This NF-κB complex ensures that the cell will survive. As shown, studies in autoimmunity have identified mutations and functional blocks in the NF-κB signaling pathway in autoimmune disease. These mutations alter the autoreactive T cells signaling due to disruptions in NF-κB activation. NK, natural killer cell; LMP2, large multifunctional peptidase 2; IKK, IκB kinase; AIRE, autoimmune regulator; SUMO4, small ubiquitin-like modifier 4; E<sub>2</sub>, 17β-estradiol; Ubc, ubiquitin-binding complex; NOD2, CARD15 gene; CK II, creatine kinase II.

Fig. 3. NF-κB controls cell death (apoptosis) and life decisions in immune cells in the periphery. If the NF-κB pathway is intact in the periphery, activated NF-κB enters the nucleus and results in the transcription of genes for survival. If the NF-κB pathway via is blocked, the cell will die instead with TNF exposure. TNF is essential in the peripheral in maintaining cell life and death decisions and control of T cell populations.



induced cytotoxicity toward target antigens. Apoptosis of cytotoxic T cells was not directly accessed in these experiments, but the functional elimination of autoreactive T cell clones suggests that death of these cells was a likely mechanism. Estriol also directly alters T cell to secrete cytokines of the T helper type 2 (Th2) phenotype, a patterning that would inhibit baseline TNF-α secretion and perhaps hamper autoreactive T cell clones (77).

Hormonal effects on NF-κB also may help to explain the sex differences seen in response to treatment. A randomized clinical trial of IFN-β in multiple sclerosis uncovered an unexpected treatment × sex interaction (62a). At two different doses, women responded better to IFN-β than men. One possible explanation may stem from IFN-β’s reliance on NF-κB, as part of a nucleoprotein complex, to activate the transcription of target genes that control cell life and death decisions. If estradiol raises levels of NF-κB, female patients might be more responsive to treatment than men because of the higher baseline concentrations of NF-κB to activate target genes.

Gene Effects on NF-κB

Genetic defects altering NF-κB activity are a common denominator across several autoimmune diseases: Type 1 diabetes, lupus, Crohn’s disease, Sjogren’s Syndrome, autoimmune regulator diseases [autoimmune polyendocrinopathy syndrome (APS)-1 or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy], and scleroderma (Fig. 2). NF-κB dysregulation has been found not only in humans but in at least two animal models of autoimmune disease. Although the particular modulator of NF-κB activity varies by disease, the diseases remarkably overlap by almost uniformly hampering NF-κB formation or functional activity in ways that are particular to the immune cell type and autoimmune disease (Table 1).

The nonobese diabetic (NOD) mouse is an animal model of two autoimmune diseases, i.e., Type 1 diabetes and Sjogren’s syndrome. Most research work on NOD mice has centered on studies related to the onset of Type 1 diabetes in this animal model, a lethal disease. This autoimmune dis-

Table 1. Autoimmune diseases associated with disruptions in NF-κB in lymphocytes

Disease	Species	Gene	Cell Type	Action on NF-κB	References
Crohn’s disease	Human	NOD2	Monocytes	Increases TLR2-induced NF-κB; reduces TNF secretion; decreases ubiquitination of NEMO	2, 19, 48, 72
		TNF	Monocytes	Prevents NF-κB activation	43
Inflammatory bowel disease	Human	TNF	Monocytes	Less TNF; less NF-κB	69
Ulcerative colitis	Human	NF-κB1 (p105/p50)		Decreased NF-κB	38
Lupus	Human	NF-κB; TNFRII		Decreased NF-κB activity	37
Type 1 diabetes	Human	NF-κB		Unknown	31
	Human/mouse	LMP2/LMP 7		Prevents activation of NF-κB	16, 18, 23, 28–30, 76
Multiple sclerosis	Human	NF-κB1; NF-κB3; NF-κBL; NF-κB1A		Unknown	50
Scleroderma	Human	CD8	NF-κB	Altered NF-κB; increased apoptosis	

NOD2, CARD15 gene; TLR2, Toll-like receptor 2; NEMO, NF-κB essential modulator; TNFRII, TNF receptor type II; LMP, large multifunctional peptidase.

ease features destruction of insulin-producing islet cells of the pancreas by autoreactive T cells. Female NOD mice are far more prone to disease onset, with a female-to-male ratio of at least 3:1. The first in a series of studies showed that diseased animals have a decreased ability to activate NF- $\kappa$ B in memory T cells, which are responsible for the direct islet destruction. In this animal model, this T cell defect is partly from the reduced expression of the protein large multifunctional peptidase 2 (LMP2), a proteasome subunit (76). The genetic defect traces to LMP2's promoter region. Reduced LMP2 expression leads to defective proteasomes, which, among other functional effects, cannot degrade I $\kappa$ B- $\alpha$  to release active NF- $\kappa$ B (29). The reduced NF- $\kappa$ B activity, as a result of a feedback loop, also curtails the activity of the LMP2 gene (75). The overall effect of having reduced NF- $\kappa$ B activity (by either mechanism) is to increase the survival of a key subpopulation of highly activated and autoreactive T cells. In what may be a hormone-gene interaction, females with the same genetic defect as males produced autoreactive T cells, have proteasomes that degrade the I $\kappa$ B  $\alpha$ -subunit less effectively, and have autoreactive T cells (29). These autoreactive T cells have a hampered ability to produce active forms of NF- $\kappa$ B. Male mice have adequate NF- $\kappa$ B activation and thus do not form autoreactive T cells. Macrophages, which are important for maintaining the ratio of different forms of T cells, have a different phenotype in the NOD mouse after certain types of cellular stimulation. With at least some forms of surface stimulation, NF- $\kappa$ B activity is found to be increased, followed by the upregulation and secretion of proinflammatory cytokines that abnormally alter the T cell repertoire (47, 60). Remarkably, a recent human study (42) of isolated peripheral lymphocytes of patients with Sjogren's syndrome uncovered a similar lack of LMP2 protein production, thereby suggesting that immune cells in Sjogren's syndrome would have less NF- $\kappa$ B activity.

Humans with Type 1 diabetes have a genetic defect separate from that in NOD mice, but the defect also decreases NF- $\kappa$ B activity. Type 1 diabetes preferentially affects males of European descent (3:2 male-to-female ratio) (25). A new mutation has been identified in a gene [suppressor of *mif* two 3 homolog 4 (SUMO4)] expressed in monocytes (27). SUMO4 encodes a protein involved in the ubiquitination of I $\kappa$ B- $\alpha$ , one of the necessary steps to form functional NF- $\kappa$ B (Fig. 2). A single-amino acid substitution defect alters NF- $\kappa$ B transcriptional activity in monocytes exposed to select stimuli. The role of this mutation in other immune cells has not yet been described. To date, expression of the SUMO4 variant has not been studied in T cells. NF- $\kappa$ B polymorphisms in the regulatory region of the NF- $\kappa$ B gene in one population-based study (31) also influenced the susceptibility to Type 1 diabetes.

In Crohn's and ulcerative colitis, inflammatory diseases of the gut, the NOD2 gene has been identified as having mutations that confer disease susceptibility (34, 52). Defects in the NOD2 protein, a new protein unrelated to the NOD mouse, alters the activity of NF- $\kappa$ B in monocytes, most likely by lessened NF- $\kappa$ B activity (1, 48, 52). Although the precise physiological role of the protein is still evolving, depending on the cell type and cell surface trigger, the bottom line is that NF- $\kappa$ B activity is perturbed in yet another autoimmune disease. Some reports (48, 72) have shown higher or lower NF- $\kappa$ B

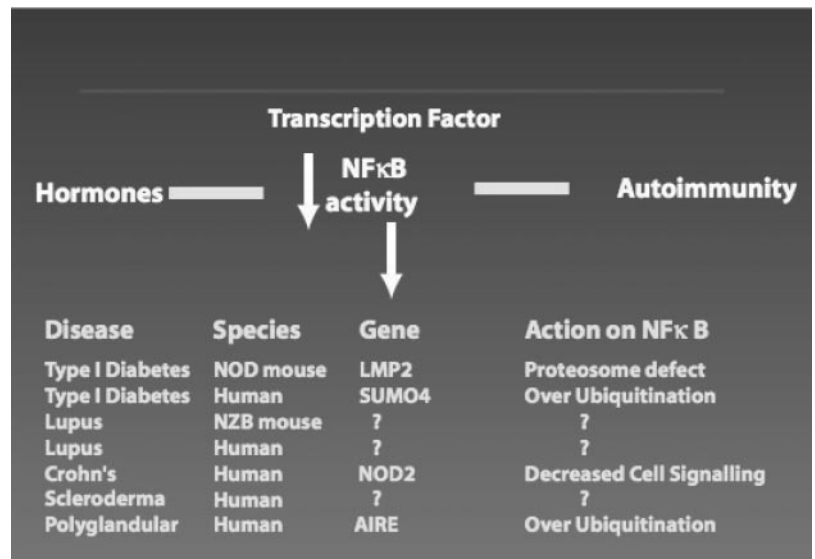
activity depending on the cell type and stimulant used to induce NF- $\kappa$ B activity. Cell surface triggers or stimulants can be naturally occurring cytokines, chemokines, or hormones. Similar to Type 1 diabetes, an ulcerative colitis-specific NF- $\kappa$ B1 promoter polymorphism influences the risk for this autoimmune disease (38). Similar to lupus, associated TNF- $\alpha$  polymorphisms contribute further to the reductions of the NF- $\kappa$ B pathway in lymphoid cells and susceptibility to Crohn's disease (43, 45).

Four other autoimmune diseases also are marked by alterations in NF- $\kappa$ B activity. Although the underlying defects vary, the common theme of altering NF- $\kappa$ B activity is consistent, and the defects sometimes also include TNF proteins. TNF works on the cell surface to activate the NF- $\kappa$ B pathway. Alterations in the levels of serum TNF, binding affinity of TNF to a possible mutant TNF receptor, and downstream intracellular steps of NF- $\kappa$ B signaling pathways have all been linked to human and murine autoimmune disease. Since the NF- $\kappa$ B pathway normally tightly regulates cell life and death decisions and controls many cytokine gene levels, single or cumulative defects could potentiate the survival of autoreactive cells. In lupus, activation of NF- $\kappa$ B signaling is attenuated in T cells due to the absence of the p65 appearance in the nucleus, one of the NF- $\kappa$ B subunits that binds to DNA (74). This is compounded in lupus by a polymorphism in TNF receptor 2, a version of the TNF receptor restricted to activated CD8 T cells. This mutation affects TNF-induced apoptosis by decreased NF- $\kappa$ B signaling and thus the set point for death (67). Finally, mutations in the AIRE gene, a single recessive mutation controlling a rare form of polyglandular autoimmunity, indicate that the AIRE protein is a ubiquitin ligase, a processing step necessary for NF- $\kappa$ B activation (32). This regulation maybe in the form of the AIRE protein itself, representing a ubiquitin ligase that alters I $\kappa$ B- $\alpha$  degradation. In an animal model of lupus, female New Zealand black mice (which are more disease prone than males) display an alteration in NF- $\kappa$ B activity upon cytokine activation of thymocytes, dendritic cells, and monocytes (47, 68). In scleroderma, NF- $\kappa$ B activity in T cells is lowered, also with heightened apoptosis of T cells upon exposure to TNF. Although the mechanisms of altering NF- $\kappa$ B are still being defined in each disease, reductions in NF- $\kappa$ B activity are correlated with higher levels of apoptosis in autoreactive T cells (CD8<sup>+</sup>) with the isolation of these cells *in vitro* (Fig. 4). This heightened apoptosis with a ligand such as TNF represents a well-known trait of cells with altered I $\kappa$ B- $\alpha$  degradation (33, 40).

Currently on the market for treatment of rheumatoid arthritis and Crohn's disease are classes of drugs that remove or inactivate serum TNF. These so-called anti-TNF therapies come in a number of different formulations *i.e.*, Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab). If the above data from diverse experiments suggest that some forms of autoimmunity may need more TNF for the death of autoreactive T cells or their specific death in the periphery after immune activation, these currently marketed forms of therapy may seem paradoxical. Although these drugs certainly can remove inflammation and thus improve the symptoms of autoimmunity, the data presented above predict that this therapy could exacerbate or



Fig. 4. Proposed role of transcription factor NF-κB in autoimmunity and the possible interplay of genes, sex, and the immune response. Recent murine and human data depict mutations in NF-κB signaling in immune cells. Although the exact proteins affected vary, many of these proteins regulate the complex process of NF-κB activation.



elicit new autoimmune disease in some patients. Indeed, neutralization of TNF by drug therapy with anti-TNF has been shown to induce, in some cases, new or exacerbated autoimmunity (Table 2).

Anti-TNF therapy has been used most broadly in rheumatoid arthritis. In some rheumatic patients, this therapy induces new forms of autoimmunity that mimic multiple sclerosis, autoimmune hemolytic anemia, Type 1 diabetes, lupus, and psoriasis (9, 11, 13, 21, 22a, 24, 35, 41, 46, 51, 61, 63, 71).

The second most common use of anti-TNF therapy is in Crohn's disease. The induction of new autoimmunity has also been observed in these autoimmune patients with this drug therapy. Again, these symptoms can range from new autoantibodies often consistent with lupus to clinical lupus (55–57, 71). Trials were also conducted with anti-TNF therapy in multiple sclerosis patients. In these human studies (55–57, 71), patients consistently reported disease worsening. In combination with the new onset demyelization, side effects of anti-TNF therapy in both rheumatoid arthritis and Crohn's disease, the data are consistent with some autoimmune patients not benefiting from the removal of TNF (20, 65).

The challenges ahead are to understand more about NF-κB and its role as a unifying pathogenic mechanism across autoimmune diseases, its role in specific immune cell types in response to different inducers, and how NF-κB may affect gene-hormone interactions and TNF signaling. This emerging area of knowledge will spur efforts to develop targeted therapies for specific autoimmune diseases or subgroups of patients. Certainly an area of important and future efforts should be studies examining the role of sex hormones in the regulation of the NF-κB pathway for T cell selection. These studies could contribute toward an understanding of why women are afflicted with more autoimmune diseases.

ACKNOWLEDGMENTS

We thank Lynne Murphy for the administrative assistance and Dr. Noel Rose for lifetime commitments to increased awareness of autoimmune diseases' disproportionate impact on women.

GRANTS

We are indebted to The Iacocca Foundation for the support of this work.

Table 2. Anti-TNF therapy induces new forms of second-degree autoimmunity

Primary Disease	Second-Degree Complications		
	Autoantibodies	New Autoimmune Disease	Reference
Rheumatoid arthritis		Psoriatic skin Autoimmune vasculitis	14, 17, 22, 39, 66, 70 24, 35
	ANA dsDNA		13, 21, 22a, 41, 46, 51, 71 46, 51
Juvenile rheumatoid arthritis		Multiple sclerosis Type 1 diabetes	63 10
Rheumatoid arthritis and spondylarthropathy	ANA; dsDNA ± nucleosome ± histone		15
Colitis		Multiple sclerosis	20
Crohn's disease	ANA; dsDNA		56–58
	ANA	Multiple sclerosis Lupus; autoimmune hemolytic anemia	20, 65 58, 71
Sjogren's syndrome	DNA	Autoimmune hepatitis	49

ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA.

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